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09/896,812	06/29/2001	Thomas D. Madden	16303-008030	6998

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/896,812
Filing Date: June 29, 2001
Appellant(s): MADDEN ET AL.

Carol Laherty
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 6-19-2006 appealing from the Office action mailed 10-3-2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,110,491	KIRPOTIN	8-2000
5,543,152	WEBB	8-1996

(9) Grounds of Rejection

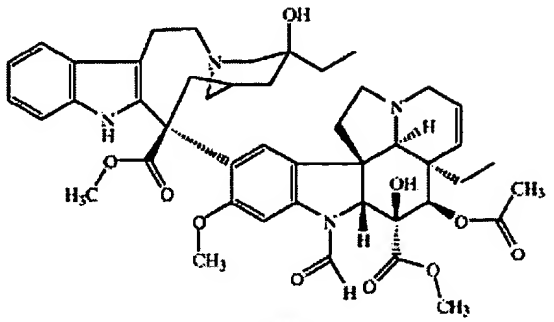
The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 36, 43 and 66-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) in combination with Webb (5,543,152).

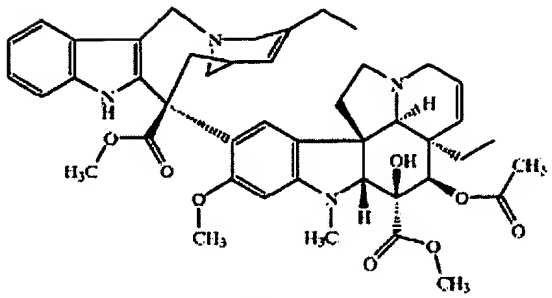
Kirpotin discloses liposomal compositions wherein the active agent is in the precipitated form. The active agent according to Kirpotin can be any compound with ionizable groups. The active agents suggested by Kirpotin are antineoplastic agents, doxorubicin, vincristin, vinblastine and vinorelbine. The liposomes are made of various phospholipids and sphingomyelin; the liposomes contain cholesterol. The lipid - drug ratios in Kirpotin also appear to fall within the claimed ratios (abstract; col. 4, line 54 through col. 6, line 18; col. 9, lines 22-67; examples and claims). Kirpotin's examples include only liposomes made from egg phosphatidylcholine and cholesterol in amounts falling within claimed ratios and not sphingomyelin; however, it would have been obvious to one of ordinary skill in the art to use sphingomyelin instead of phospholipid in the liposomes since Kirpotin is suggestive of the use of sphingomyelin and provides guidance as to how to make these liposomes. The use of sphingomyelin along with cholesterol would also have been obvious to one of ordinary skill in the art since Webb teaches several advantages of liposomal formulations based on sphingomyelin and cholesterol (in instant amounts). According to Webb, these liposomes are much more stable to acid hydrolysis, significantly better drug retention characteristics, better loading characteristics into tumors and Webb teaches the applicability of the liposomes to a variety of lipophilic drugs, vinca alkaloids in particular (abstract, col. 4, line 18 through

col. 5, line 34, examples and claims). Although both Kirpotin, and Webb lack the specific teachings of camptothecins, it would have been obvious to one of ordinary skill in the art to use any lipophilic drug including camptothecins with a reasonable expectation of success since both teach the applicability to lipophilic drugs and Webb in particular teaches the advantages which relate to liposomes containing sphingomyelin and cholesterol themselves.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that presently claimed invention is directed to specific liposomal vinorelbine composition having superior properties. Applicant further argues that the liposomal vinorelbine formulations having the claimed features possess superior pharmacokinetic properties, including slower drug release. According to appellant, the examiner has failed to identify where either Kirpotin or Webb describe a liposomal vinorelbine formulation having a vinorelbine to lipid ratio of 0.1 – 0.5: 1 (w/w). Further according to appellant, Webb fails to describe vinorelbine at all, and when describing liposomal formulations comprising vincristine, Webb indicates that vincristine may be present at a drug: lipid ratio in the range of approximately 0.01 – 0.2: 1 and this range is substantially different from the presently claimed range of 0.1 – 0.5: 1. These arguments are not persuasive. First of all, the examiner respectfully points out to the board that the structures of vinca alkaloids, vincristine, vinblastine and vinorelbine are very closely related and therefore, one of ordinary skill in the art would expect similar encapsulation of these compounds in the liposomes (see below for structures).



Vincristine



Vinorelbine

Therefore, it is the examiner's position that Webb's observations with vincristine encapsulated within liposomes containing sphingomyelin and cholesterol at a 75/25 mol % to 30/50 mol % (same mol % as in instant invention) are equally applicable to vinorelbine. In response to appellant's arguments regarding the presently claimed range of drug: lipid ratios, the examiner points out that Webb's vincristine amounts of 0.01 to 0.2 falls within instant vinorelbine amounts of 0.1 to 0.5. Appellant argues that it is clear that it is not mere oversight that leads Webb to describe such a low and narrow drug: lipid ratio for vincristine, since in a related continuation – in- part application (5,741,516), the drug: lipid ratio described for swainsonine is 0.01 – 0.5: 1, which is a much broader range. Therefore, according to appellant, the conclusion to be drawn from Webb appears to be that different drugs will have different preferred drug: lipid ratios. This argument is rather confusing since Webb teaches ranges and not a specific amount of vincristine, which is drastically different from the amount for swainsonine. If for example, Webb teaches 0. 01 moles for vincristine and 0.5 moles for swainsonine, then

one could come to the conclusion from Webb that different drugs have different preferred drug: lipid ratios. However, Webb teaches ranges which overlap and therefore, appellant's arguments are not persuasive.

Appellant argues that Kirpotin specifically recites vinorelbine in a long list of ionizable compounds that might be used in certain liposomal formulations and that Kirpotin is completely silent with respect to vinorelbine: lipid ratios. According to appellant, the only drug: lipid ratios described in Kirpotin are for the compound doxorubicin and that the range is 0.008 – 0.246: 1 (mol/mol) which is different from instant 0.1 – 0.5: 1 (w/w) ratio recited in instant claims. The examiner disagrees. Taking the molecular weights of doxorubicin (580) and sphingomyelin (299.5), when converted to w/w ratios, the range taught by Kirpotin corresponds to 0.01 – 0.5: 1 (w/w) and this range certainly overlaps instant range of 0.1 – 0.5: 1. The calculated w/w ratios of doxorubicin to phospholipid which are given in mg drug/mmol of phospholipids in Tables in Examples 7 and 8 in Kirpotin, taking the above molecular weights for doxorubicin and sphingomyelin correspond to 0.02 – 0.3: 1 and 0.05 – 0.47: 1 respectively and these ratios also overlap instant ratios. Appellant argues that even assuming arguendo that this is true, the recitation of one or more different doxorubicin: lipid ratios clearly does not amount to a description of a vinorelbine: lipid ratio of 0.1 – 0.5: 1 (w/w). The examiner disagrees. Although doxorubicin is exemplified, Kirpotin is suggestive of the applicability of the liposomes even for vinca alkaloids, vincristine, vinblastine and claimed vinorelbine. Therefore, one of ordinary skill in the art would be motivated to use the ratios taught by Kirpotin even for vinca alkaloids including vinorelbine.

Appellant argues that not all lipid formulations are equal for drug delivery purposes, and the optimal drug: lipid ratios vary for different drugs. The examiner agrees, but points out that the cited references of Kirpotin and Webb provide guidance as to the drug – lipid ratios which could be used and suggestive of the applicability of these ratios even to vinca alkaloids including vinorelbine and one of ordinary skill in the art use these ratios or vary the prior art ratios with a reasonable expectation of success. Appellant has shown no unexpected results although argued by appellant that all of the claimed liposomal vinorelbine formulations provide unexpected advantageous pharmacokinetic properties including enhanced drug retention and that the liposomal vinorelbine formulations of claim 68 exhibits the greatest enhancement of drug retention as shown in Figures 1 A and 2 A. Specifically, appellant argued in response to the first office action that as the Figures show that as the drug: lipid ratio is increased from 0.1: 1 to 0.2:1 to 0.3: 1, there is a corresponding increase in drug retention, which is. associated with drug precipitation in the liposomal interior and that there is a corresponding reduction in the blood clearance half-life for vinorelbine. According to appellant as is understood in the art and described in the instant specification, a slower release rate and slower blood clearance half-life is preferable and more efficacious, particularly in the treatment of tumors, including those typically treated with vinorelbine. Thus, the claimed liposomal vinorelbine formulations, having a drug: lipid ratio of 0.1-0.5: 1 (w/w), such that at least 50% of the total vinorelbine is precipitated, are identified according to the instant specification, possess previously unrecognized advantages and, thus, are not obvious in light of the cited art". These arguments are not persuasive.

First of all, it should be pointed out that though doxorubicin is used in the examples, on col. 6, line 18 Kirpotin clearly teaches the applicability of precipitation to vinca alkaloids, vinorelbine and vincristine. Through examples shows that the greater amounts of the drug are encapsulated in a precipitated state than the drug in unprecipitated state (129 nmoles/micromole phospholipid as opposed to 8 nmoles/ micromoles of phospholipid, see example 1). The increase in drug retention for vinorelbine is to be expected from Kirpotin's teachings and not an unexpected result. Secondly, the same claimed pharmacokinetic advantages of using SM/cholesterol in claimed ratios for vinca alkaloids are clearly evident from col. 9 of Webb. According to Webb, the leakage of vincristine from DSPC/chol. Is very rapid and in contrast its leakage from SM/chol. Liposomes was much slower, with a greater than 60 % of the entrapped drug remaining in the liposomes 24 hours after the injection. Therefore, what is observed by appellant is an expected result from the teachings of Kirpotin and Webb and not an unexpected finding.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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